

Novel Humanized Peripheral Blood Mononuclear Cell Mouse Model with Delayed Onset of Graft-versus-Host Disease for Preclinical HIV Research.

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Public Summary:

Currently, there is no cure or vaccine for HIV infection; thus, continued research is needed to end the HIV pandemic. While many animal models are used in HIV research, none is used more than the humanized mouse model. A major limitation with current humanized mouse models is the development of graft-versus-host disease (GVHD). Here, we describe a novel humanized-peripheral blood mononuclear cells (PBMC) mouse model that has a delayed onset GVHD development and supports and models HIV infection comparably to well-established humanized mouse models. This model is a new valuable tool in HIV research.

Scientific Abstract:

Humanized mouse models are based on the engraftment of human cells in immunodeficient mouse strains, most notably the NSG strain. Most used models have a major limitation in common, the development of graft-versus-host disease (GVHD). GVHD not only introduces variabilities into the research data but also leads to animal welfare concerns. A new mouse strain, B6.129S-Rag2(tm1Fwa) CD47(tm1Fpl) IL2rg(tm1Wjl)/J, which lacks Rag1, IL2rg, and CD47 (triple knockout [TKO]), is resistant to GVHD development. We transplanted TKO mice with human peripheral blood mononuclear cells (PBMCs) to establish a new humanized PBMC (hu-PBMC) mouse model. A cohort of these mice was infected with HIV-1 and monitored for plasma HIV viremia and CD4(+) T cell depletion. The onset and progression of GVHD were monitored by clinical signs. This study demonstrates that TKO mice transplanted with human PBMCs support engraftment of human immune cells in primary and secondary lymphoid tissues, rectum, and brain. Moreover, the TKO hu-PBMC model supports HIV-1 infection via the intraperitoneal, rectal, or vaginal route, as confirmed by robust plasma HIV viremia and CD4(+) T cell depletion. Lastly, TKO mice showed a delayed onset of GVHD clinical signs (approximately 24 days) and exhibited significant decreases in plasma levels of tumor necrosis factor beta (TNF-beta). Based on these results, the TKO hu-PBMC mouse model not only supports humanization and HIV-1 infection but also has a delayed onset of GVHD development, making this model a valuable tool in HIV research. **IMPORTANCE** Currently, there is no cure or vaccine for HIV infection; thus, continued research is needed to end the HIV pandemic. While many animal models are used in HIV research, none is used more than the humanized mouse model. A major limitation with current humanized mouse models is the development of graft-versus-host disease (GVHD). Here, we describe a novel humanized-PBMC mouse model that has a delayed onset GVHD development and supports and models HIV infection comparably to well-established humanized mouse models.

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